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Coeliac disease and HLA-conferred susceptibility to autoimmunity are associated with IgE sensitization in young children

To the Editor,

The prevalence of immune-mediated diseases is continuously rising.[1,2] In addition to genetic predisposition, socioeconomic circumstances and environmental factors may modulate the development of these diseases. Although the mechanisms leading to abnormal immune responses in autoimmune and allergic diseases may share some common pathways, the detailed pathogenesis of these conditions are still inadequately understood. The results on co-existence of allergic and autoimmune diseases have been hitherto inconsistent, some indicating co-existence[3,4] and others the opposite or no relationship at all.[5,6]

The aim of the current study was to examine the relationship between allergen-specific IgE (sIgE) sensitization patterns, human leukocyte antigen (HLA)-conferred disease susceptibility, and autoimmunity-associated outcomes in Finland, Estonia, and Russian Karelia. These three geographically adjacent areas represent socioeconomically diverse countries with only modest differences in frequencies of HLA haplotypes conferring risk for type 1 diabetes (T1D) and coeliac disease (CD),[7] but they differ remarkably in the prevalence of immune-mediated diseases.[8]

Children born in Finland, Estonia, and Russian Karelia were observed prospectively either from birth up to the age of 3 or from 3 to 5 years of age. Children in the birth cohort (BC; n=714) carried HLA-conferred susceptibility to T1D and CD; either a combination of DR3-DQ2 and DR4-DQ8 haplotypes or alternatively DR4-DQ8/X (X=DR4-DQ8 or a neutral haplotype) or DR3-DQ2/Y (Y=DR3-DQ2 or a neutral haplotype) genotypes. Children in the young children's cohort (YCC; n=3580) represented the general

population, with no selection based on HLA genotype. The participants were monitored for the appearance of sIgEs (≥0.35 kU/l) against dietary (egg, milk, peanut) and aeroallergens (cat, dog, dust mite, birch, timothy), signs of T1D-associated islet autoimmunity (IA) or CD-associated tissue transglutaminase antibody (tTGA) positivity and progression to clinical T1D or CD. Detailed methodology is provided in the Supporting Information.

A total of 37.5% of children in the BC and 39.4% in the YCC had been sensitised to at least one specific allergen during the respective follow-up (Table S1). Both cohorts showed similar proportions of dietary allergen sensitisations (88.1% vs. 83.3% of the sensitised), but sensitised children in the BC were less often sensitised to aeroallergens (41.0% vs. 63.6%, $P<0.001$) and to both dietary and aeroallergens (29.1% vs. 46.9%, $P<0.001$). Finnish children developed allergen-specific sensitisation most frequently, followed by Estonian and Russian Karelian participants (Table 1). Sensitisation rates were higher among males than among females in both cohorts ($P<0.02$). The distributions of HLA risk groups did not differ between sensitised and non-sensitised children in either cohort.

At the age of 3 years, 38.5% of the BC children and 30.2% of the YCC children had at least one positive sIgE ($P<0.001$; Figure 1A). This difference was seen especially in Estonians (34.2% vs. 27.2%, $P=0.035$) and weakly in Finns (41.2% vs. 35.1%, $P=0.057$). A similar difference was observed for dietary allergen sensitisation at the age of 3 years (31.7% vs. 24.1% in BC and YCC respectively, $P<0.001$; Figure 1B), being also present in Finns (34.7% vs. 28.7%, $P=0.046$) but not clearly so in Estonians (27.1% vs. 21.3%, $P=0.061$). Aeroallergen sensitisation at 3 years was more frequent in the BC children than in the YCC children (18.7% vs. 13.1%, $P=0.001$; Figure 1C; in Finland 20.4% vs. 15.5%, $P=0.045$; in Estonia 16.4% vs. 11.6%, $P=0.048$).

When combining both cohorts, at the age of 3 years males were more frequently sensitised to at least one specific allergen compared to females (33.1% vs. 29.2%, $P=0.009$; dietary allergens 25.8% vs. 24.3%, $P=0.288$; aeroallergens 14.8% vs. 12.7%, $P=0.053$). Children with HLA risk genotypes for T1D and CD were more frequently sensitised compared to children with HLA risk groups associated with neutral or protective effect on the disease risk (34.2% vs. 30.3%, $P=0.016$); also seen in sensitisation to dietary allergens (27.8% vs. 24.3%, $P=0.025$), but not in sensitisation to aeroallergens (15.2% vs. 13.3%, $P=0.125$).

Sensitised children in both the BC and the YCC had higher odds to test positive for tTGA during their respective follow-up, compared to non-sensitised children (Table 1). In the YCC, sensitised children had also over six times the odds to be diagnosed with CD during the follow-up.

In contrast to other studies that have reported co-occurrence of atopic sensitization and T1D,[3,4] we did not observe any correlation between sIgE sensitisation and T1D or IA. In the current study, sensitised children did, however, have higher risk for CD and tTGA positivity in contrast to a Swedish study that

reported no co-existence between self-reported allergies and CD.[6] As sIgE sensitisation at the age of 3 years was more frequent in children with HLA-conferred risk genotypes compared to children without these risk genotypes as well as compared to the general population, these results demonstrate that atopic and autoimmune diseases can be co-occurring. Our results support the idea of a common denominator in allergic and autoimmune diseases that may be especially crucial in early childhood, when the immune system is not yet fully mature. Since sIgE sensitisation was associated with HLA-conferred susceptibility to T1D and CD, but clinically only to CD and its associated autoimmunity, one might speculate that the pathomechanisms of atopic sensitisation share more common pathways with CD than with T1D.

The prospective study setting, with the interesting pools of children genetically at-risk vs. the general population allowed us to compare these two cohorts at the age of 3 years. One has to keep in mind that sIgE alone does not indicate clinical allergy, but together with positive skin prick tests and consistent allergy symptoms, they form a more accurate risk profile for future allergies. Poor study compliance in Russian Karelia in both cohorts were unfortunate and did not allow us to perform proper analyses between all three countries at all ages.

To conclude, we found that children carrying HLA genes predisposing to T1D and CD are more frequently sIgE sensitised at 3 years of age. We also observed that sensitisation to common allergens increases the risk of positivity for tTGA and for CD, but not for IA or T1D. The contemporaneous occurrence of atopic markers and autoimmune diseases suggests that these diseases may share some common pathogenic features.

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Conflict of Interest

The authors declare no conflict of interest.

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TABLE 1 Demographic and clinical characteristics of IgE sensitized and non-sensitized children. Values are medians and interquartile ranges if not otherwise indicated.

	Birth cohort			Young children's cohort		
	sIgE sensitized n=268	Non-sensitized n=446	*P*	sIgE sensitized n=1412	Non-sensitized n=2168	*P*
Proportion of males (%)	57.8	48.2	**0.016**	54.5	50.2	**0.015**
Country (%)			**<0.001**			**<0.001**
Finland	45.6	54.4		46.0	54.0	
Estonia	32.4	67.6		36.9	63.1	
Russian Karelia	15.9	84.1		21.7	78.3	
Maternal age at birth, years	30.6 (27.1–33.8)	29.9 (25.9–33.7)	0.087	30.6 (26.8–33.9)	30.1 (25.7–34.0)	**0.021**
Number of siblings at birth	0 (0–1)	1 (0–1)	0.231	0 (0–1)	1 (0–1)	0.070
Gestational age, weeks	40.1 (39.3–41.0)	40.1 (39.1–41.0)	0.939	40.0 (39.0–40.9)	40.0 (39.0–40.7)	**0.004**
Caesarean section (%)	8.6	11.0	0.366	21.0	19.7	0.346
Birth weight, g	3610 (3230–3910)	3589 (3273–3889)	0.768	3560 (3230–3930)	3534 (3200–3890)	0.116
Birth length, cm	51 (49–52)	51 (50–52)	0.778	51 (49–52)	51 (49–52)	0.665
HLA risk group (%)			0.783			0.543

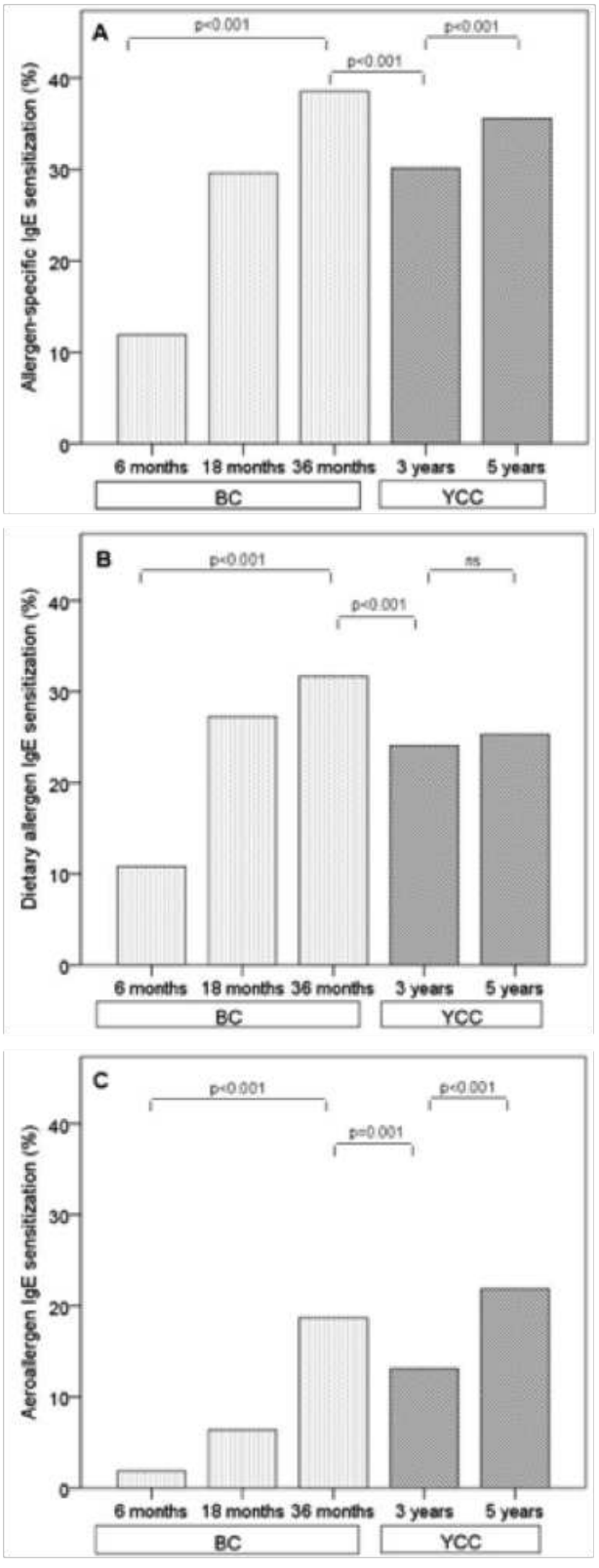
DR3-DQ2 / DR4-DQ8	10.1	8.5		1.9	1.4	
DR4-DQ8 / X [a]	33.6	34.1		6.3	7.0	
DR3-DQ2 / Y [b]	56.3	57.4		11.2	10.9	
non-risk genotypes	–	–		80.6	80.7	
Clinical outcomes [% (n)]						
Islet autoimmunity [c]	6.7 (18)	6.1 (27)	0.846	6.2 (88)	4.7 (102)	0.055
Type 1 diabetes	1.5 (4)	1.6 (7)	1.000	0.5 (7)	0.5 (11)	1.000
Positivity for tTGA	3.7 (10)	0.7 (3)	**0.008** [d]	1.8 (25)	0.7 (16)	**0.007** [e]
Coeliac disease	2.2 (6)	0.7 (3)	0.142	1.1 (16)	0.2 (4)	**<0.001** [f]

[a] X=DR4-DQ8 or a neutral haplotype; [b] Y=DR3-DQ2 or a neutral haplotype; [c] positivity for insulin autoantibodies or antibodies to glutamic acid decarboxylase, islet antigen 2, or zinc transporter 8; [d] OR 5.7 (95CI 1.6–21.0); [e] OR 2.4 (95CI 1.3–4.6); [f] OR 6.2 (95CI 2.1–18.6)

sIgE, allergen-specific immunoglobulin E; HLA, human leukocyte antigen; tTGA, tissue transglutaminase antibody; OR, odds ratio; 95CI, 95% confidence interval

Figure legend

FIGURE 1 Proportion of children with allergen-specific IgE in the birth cohort (BC) at 6, 18, and 36 months and in the young children's cohort (YCC) at 3 and 5 years of age. At 3 years of age, children in the BC, who all carried HLA-conferred risk to type 1 diabetes and coeliac disease, were more frequently sensitized to A) any allergen (P<0.001), B) dietary allergen (P<0.001), and C) aeroallergen (P=0.001) compared to children in the YCC who represented the general population. In both cohorts, sensitization rates increased by age, with the exception of dietary allergen sensitization between 3 and 5 years of age in the YCC.



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